UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,263	04/18/2006	Gerard M Housey	395/61	6621

26646 7590 06/07/2010

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
06/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/541,263	HOUSEY ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 May 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *12 May 2010*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See *Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *16-24*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Continuation of 3. NOTE: The amendment to claim 16 recites "d)determining that the small molecule binds to IRS2 or to a complex comprising IRS2 and other cellular proteins and cannot bind to the non-IRS2 proteins in the absence of IRS2. Applicants state support for this amendment can be found at paragraph [0032]. Paragraph [0032] recites:

By upregulation of IRS2 function is meant an increase in the amount of IRS2 protein within a cell or enhancing IRS2-mediated signal transduction by activators as defined herein. By activator or inhibitor of IRS2 is meant a small molecule that binds to IRS2 alone and activates or inhibits the signaling function of IRS2, or a small molecule that binds to a complex comprising IRS2 and other cellular proteins and wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2. By reduction or downregulation of IRS2 function is meant a decrease in the amount of IRS2 protein within a cell or reduced IRS2-mediated signal transduction by inhibitors as defined herein.

Paragraph [0032] defines "small molecule" as activator or inhibitor of IRS2 that binds to IRS2 alone and activates or inhibits the signaling function of IRS2, or a small molecule that binds to a complex comprising IRS2 and other cellular proteins and wherein said small molecule cannot bind to the non-IRS2 proteins in the absence of IRS2. In other words, paragraph [0032] describes this inability to bind to non-IRS2 proteins as an innate characteristic of the small molecule but does not teach how this characteristic is to be determined. The insertion of this characteristic in the "determining" step changes the claims' meaning from the characteristic of the small molecule to a quality that is determined by the assay. There is no support for this in the specification. Paragraph [0051] discusses cAMP assays; paragraphs [0052] and [0055] discuss assays for upregulation of IRS2; paragraph [0053] discusses assays that stimulate IRS2 signlaning; paragraphs [0054], [0067] and [0069] discuss phosphoyrlation assays; paragraphs [0056] - [0058] and [0061] discuss treatment of patients; paragraph [0059] discusses assays of identifying and using compounds that inhibit IRS2 in beta cells; pararaph [0060] discusses methods of identifying and using compounds that block interaction of IRS2 with degrading enzymes in beta cells and other cell types; paragraph [0062] discuss methods of identfying and using IRS2 promoting compunds to reverse catabolism during acute trauma; paragraph [0068] discusses methods of identyfing and using IRS2 promoting compounds to prevent inuslin resistance; paragraph [0064] discusses assays that up-regulate IRS2 levels in beta cells; paragraph [0065] disucsses assays that inhibit components of the IRS2 signaling cascade; paragraph [0066] discusses methods of identfying compounds that suppress inhibition of IRS2 in beta cells; paragraph [0068] discusses methods that inhibit ubiquitination of IRS2 in beta cells. Nowhere in the specification is it discussed how it is "determined" that the small molecule binds to IRS2 alone. Further, the aforementioned paragraphs discuss the assays in very general terms, stating that one skilled in the art could carry out such assays, without fully describing them.

Continuation of 11. does NOT place the application in condition for allowance because:
Regarding 112,second paragraph, even if the proposed amendement was entered, some consideration would have to be given to whether the "determining" step in d) of amended claim 16 actually is an active step. The step may read on a thought process. THe phrase "essentially does not produce" is still vague and indefinite in claim 21.

Regarding the rejection under 35 U.S.C. 103, Applicants argue that:
1) Neither the '701 patent nor the '655 patent disclose or suggest the concept of linking a compound that binds to IRS2 with the ability of the compound to modulate a defined cellular activity correlated with IRS2 but not (previously) demonstrated to be modulated by compounds that bind to IRS2.
2) It is by the methods of the present invention that one distinguishes between compounds that bind to and modulate IRS2 activity in the cell, versus compounds that either bind to IRS2 but do not modulate its activity, or compounds that modulate the IRS2 signal transduction cascade (IRS2 branch activity) in cells but do so by modifying the biological effects of other intracellular protein or non-protein targets in this pathway.
3) The Applicants point out that modulation of a target protein's activity by a compound may be direct (i. e., the compound binds to and modulates the activity of a target protein) or indirect (i. e., the compound binds not to the target protein but to another cellular component to exert its effect). Distinguishing between direct and indirect modulation of a target protein is problematic with targets like IRS proteins, which are "docking" proteins. IRS proteins link the Insulin Receptor to other intracellular proteins in order to transduce the insulin signal, but have no intrinsic enzymatic activity that can be exploited.
4) Applicants argue that the Examiner has mistakenly cited in the '701 patent to suggest that the term "IRS2 binding ligand" of the '701 patent can be equated with "compound" of the instant invention. An IRS-2 binding ligand as discussed in the '701 patent refers to a naturally occurring protein ligand such as the Insulin Receptor ('701 patent, col. 6, lines 65-68). This is distinct from the small molecule test compound described in the instant application.
5) Applicants argue that the '701 patent remains silent with respect to whether or not the compound that causes modulation of the interaction between the IRS2 polypeptide and the IRS2 binding ligand does so by binding to IRS2, the IRS2 binding ligand, another protein or non-protein species present in the assay mixture, or simply modifies the solvent system or chelates or otherwise interferes with necessary ionic components of the assay milieu such that the interaction between IRS2 and the IRS2 binding ligand is altered in some manner.
6) Applicants argue that the '655 patent focuses on target proteins evoking responsive changes in cells when overproduced. The presence of the target protein in a cell causes an observable phenotype whose intensity is related to the level of the activity of the target protein in the cell (i. e., the level of the protein and its specific activity in the presence of a modulator). In this regard, the Examiner has suggested, based on the '701 patent, that IRS2 overexpression results in increased proliferation when IL-4 is added and that this could be the basis for a screening method that identifies compounds that modulate IRS2 function. (Office Action at p. 14). To the contrary, such a method would not distinguish modulators that act on IRS2 (or a complex containing IRS2) from modulators that act on other cellular components.
7) Further, one of ordinary skill in the art would recognize that screening method disclosed in the '655 patent makes use of the intrinsic enzymatic activity of a cellular enzyme to evoke a phenotype that responds both to the level of the protein and the activity of a protein as modulated by activators or inhibitors that act on that protein to identify modulators of that protein. IRS2 does not have such an activity nor does it evoke such a phenotype.

Regarding argument 1, the '701 patent teaches a method of determining whether a compound promotes (i.e., activates) or inhibits binding of an IRS2-binding protein to IRS2 by administering the compound to the test cells which over-expresses IRS2 and measuring the binding activity (see column 6, lines 62-67 through column 7, lines 1-10). The proposed amendment of claim 16 recites a method of determining whether a small molecule (i.e., a compound) activates (i.e., promotes) or inhibits IRS2 comprising administering the small molecule to test cells which over-express IRS2 relative to control cells and causing the small molecule to come into contact with the IRS2, examining the test cell for modulation and determining that the compound binds to IRS2. Both the proposed amendment of claim 16 and the current recitation of claim 16 encompass an assay as is taught in the '701 patent. The only deficiency in the '701 patent is the implied comparison to control recited in step a). The '655 patent teaches comparison between test and control. Regarding arguments 2-3, it appears Applicants are arguing limitations not present in the claims; there is no such recitation of signal transduction or direct or indirect modulation in the claims. Regarding argument 4, the Examiner is not equating the IRS2 binding ligand or IRS2 binding protein of the '701 patent with the compound or small molecule test compound of the instant invention. Looking to the rejections made in the previous Office actions, "IRS2 binding ligand" or "IRS2 binding protein" was equated with the "complex" (see for instance, p. 6 of the 24 February 2009 rejection); in other words, the complex was IRS2 and its receptor. The small molecule that activates or inhibits IRS2 is taught at paragraph [0023] of the instant specification as being identified by measuring the amount of the IRS2 binding protein bound to IRS2. This reads upon the binding assay taught in the '701 patent. Regarding arguments 6 and 7, this leads away from the issue at hand, namely, that the '655 patent teaches the comparison with control. The '701 patent already teaches all the elements of the claims EXCEPT for the comparison to control. Further, regarding the argument that IRS2 overexpression results in increased proliferation when IL-4 is added and that this would not distinguish modulators that act on IRS2 (or a complex containing IRS2) from modulators that act on other cellular components, this leads away from the issue that the '701 patent teaches a method of determining whether a compound promotes (i.e., activates) or inhibits binding of an IRS2-binding protein to IRS2 by administering the compound to the test cells which over-expresses IRS2 and measuring the binding activity (see column 6, lines 62-67 through column 7, lines 1-10) and that claim 16 recites a method of determining whether a small molecule (i.e., a compound) activates (i.e., promotes) or inhibits IRS2 comprising administering the small molecule to test cells which over-express IRS2 relative to control cells and causing the small molecule to come into contact with the IRS2, examining the test cell for modulation and determining that the compound binds to IRS2.

The proposed amendment would overcome some of the issues under 35 U.S.C. 112, second paragraph. If the proposed amendment was entered, it would overcome the 112, second paragraph rejection of claim 18 (lack of antecedent basis for "protein of interest"; claims 19-23 (lack of antecedent basis for "host cell"); part of the issue raised for claim 21 (the recited "protein" is vague). If the proposed amendment was entered, the 102 rejection over claim 17 would be overcome since claim 17 is cancelled.